Design and Development of Cleaner Synthetic Methodologies for N,O-containing Heterocycles using Transition Metal Catalysis.

A
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BY

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UNDER THE GUIDANCE OF
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DEPARTMENT OF CHEMISTRY

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PROPOSAL FOR TOPIC APPROVAL TO BE SUBMITTED TO THE UNIVERSITY OF MUMBAI FOR THE PH.D. DEGREE IN THE SUBJECT OF **CHEMISTRY.**

Title of the topic	:	"Design and Development of Cleaner Synthetic Methodologies for N,O-containing Heterocycles using Transition Metal Catalysis"
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1. Title:

"Design and Development of Cleaner Synthetic Methodologies for N,O-containing Heterocycles using Transition Metal Catalysis"

2. Aims of the study:

To design and develop simple and efficient synthetic methodologies for functionalized *N,O*-containing heterocycles using transition metal catalysts and ligand and their applications in pharmaceuticals.

3. Objective of the study:

The objectives of the present studies are as follows:

- Designing of synthetic routes for N,O-containing heterocyclics having pharmaceutical importance
- optimization of efficient, safe, and environmentally benign catalysts and mild reaction conditions
- Synthesis of the designed target heterocyclic compounds
- Structural investigations of the prepared compounds using spectroscopic techniques
- Evaluation of therapeutic and photophysical properties of synthesized molecules ,

Introduction:

Heterocyclic compounds constitute the largest and most diverse family of organic compounds with chemical, biomedical, and industrial significance. Nitrogen and Oxygen containing heterocyclic compounds are an important class of heterocyclic compounds that have paid a significant contribution to medicinal chemistry. The types of compounds depend upon the number of nitrogen and oxygen atoms and their position in the ring.

Design and development of new catalytic synthetic methods for bioactive heterocyclic compounds following the principles of green chemistry that satisfy increasingly stringent environmental constraints are in great demand by the pharmaceutical and chemical industries. In addition, novel catalytic procedures are necessary to produce the emerging classes of heterocyclic compounds that are becoming the targets of molecular and biomedical research.

Several types of substances such as enzymes, surfactants, ionic liquids, clays, and supercritical solvents are now widely recognized as practical alternatives to traditional organic synthesis and as convenient solutions to certain intractable synthetic problems. This is due to problems associated with prevailing catalysts like hazardous nature, expensive, difficult to handle, tedious work up, requirement of hazardous organic solvents and elevated temperature conditions, and above all, their adverse effects on the environment [1].

Transition metal catalysts have become widely adopted as useful tools in modern synthetic organic chemistry because of their diverse reactivity in enabling various molecular transformations. The chemistry has expansively grown along with the development of supporting ligands, which significantly affect the reactivity and stability of the metal complexes in the primary coordination sphere. The chemistry of transition metals is extremely rich because it can easily access different oxidation states allowing them to act through one-electron or two-electron processes. As a result, both radical pathways and powerful two-electron bond-forming pathways *via* organometallic intermediates, similar to those of palladium, can occur. In addition, in copper and other metals, the different oxidation states associate well with a large number of different functional groups *via* Lewis acid interactions or π-coordination. In total, these features confer a remarkably broad range of activities allowing copper and other metals to catalyze the oxidation and oxidative union of many substrates.

In this context, our efforts will be directed towards the design of novel reaction methodologies and developing processes for the synthesis of new as well as known N,O-containing heterocyclic compounds having medicinal importance. The use of efficient, economical, and recyclable transition metal catalysts for the multicomponent synthesis of N,O-containing heterocycles *viz*. Pyrimidine, Thiazolidine-4-one, Imidazopyridine, Quinoxaline, imidazole, and Quinoline derivatives will be in prime focus. On the other hand, reactions in an aqueous medium or solvent-free conditions will also be favored.

4. Study Background (Literature Review) and significance of the study:

Transition metal catalysis is a reliable and well-established, but constantly evolving field of research. Over the past decade, single-electron strategies have emerged as powerful methods for accessing previously unattainable reactivities in transition metal catalysis, especially in the contexts of cross-coupling for carbon-heteroatom bonds formation and the construction of

alkyl–alkyl bonds. There are several transition metal salts and complexes *viz.* Cu, Ni, Pd, In, and Fe have been used for C-C bond-forming reactions. Ligands are also playing a vital role in many coupling reactions [2] and hence, ubiquitously known to be used in the field of catalysis and organic chemistry. Various ligands have been studied for coupling reactions using nickel as a catalyst such as 8-hydroxy quinoline [3], 1,2-bis(diphenylphosphino)ethane (dppe) [4], trans-1,2-diaminocyclohexane, 1,10-phenanthroline, N-phenyldiethanolamine, 1,10-bis(diphenylphosphino)ferrocene (dppf), naphthaldehyde thiosemicarbazone, and 1,4-bis(dicyclopentylphosphino)butane, etc [5].

Recently, Sonawane and coworkers reported [Ni(quin)$_2$]-catalyzed-catalyzed N-formylation and N-acylation of amines using DMF and N,N-dimethylacetamide (DMA) in homogeneous medium [6]. Furthermore, O-formyl and O-acyl protection of alkanolamines, and phenoxyethanols have been developed using Ni-(II) and Cu-(II) complexes with 8-hydroxyquinoline in homogeneous medium [7].

Thus, this strategy can successfully be employed for the development of simple, efficient, and selective methods for the synthesis of pharmaceutically important heterocyclic scaffolds as well as the widely used organic transformations.

5. International status:

Worldwide transition metal catalysis has become widely adopted as a useful tool in modern synthetic organic chemistry because of its diverse reactivity in enabling various organic transformations. The chemistry of transition metal catalysis has expansively grown along with the development of various supporting ligands, which significantly affect the reactivity and stability of the metal complexes [8].

6. National Status:

Many researchers in India also working on the development of synthetic routes for the construction of complex organic molecules and bioactive heterocyclic compounds via C-C and C-X bond formation using transition metal catalysis. Recently, Sangita Jagtap and her research group reported various organic transformations using transition metal complexes such as Copper (II) and Nickel (II) complexes [2,5].

7. Study Hypotheses:

Recently Heterogeneous catalysis is one of the fastest developing branches of chemistry. Moreover, it is strongly connected to popular environment-related applications. Palladium-catalyzed reactions commenced at the beginning of 1900, but until 1960 Pd chemistry remained largely unexplored. Afterwards, Pd catalysis received great attention and momentum due to its high catalytic activity, versatility, and ability to tune the reaction conditions. The exploration of other transition metals such as Rh, Ir, and Ru as catalysts also began in the 1920. But the use of these metals had many drawbacks such as toxicity, high price, and low abundance. Hence the focus was turned toward much cheaper and cost-effective metal catalysts. In this context, copper chemistry has great importance owing to its low cost, high functional group tolerance, high abundance, and low toxicity [9]. The diversity of copper chemistry is due to its (i) variable and interchangeable oxidation state (ii) capacity to coordinate with heteroatoms, and (iii) ability to activate terminal alkynes. These eminent qualities of copper have been well exploited in various reactions such as Ullmann coupling, Ullmann–Goldberg coupling, Ullmann diaryl ether formation, Ullmann–Hurtley condensation, Cadiot–Chodkiewicz reaction, Chan–Lam reaction, etc. The C—C and C—N bond formations serve as the backbone of these reactions.

In recent years, we have observed tremendous activity in the development of new Ni-catalyzed reactions, resulting in numerous fascinating applications in synthetic organic chemistry. Ni-catalyzed cross-coupling of electrophiles (organic halides and pseudohalides) with carbon nucleophiles (organometallic compounds) has had a prominent impact on organic synthesis [38]. Different organometallic compounds were successfully employed in the Kumada–Corriu (magnesium), Suzuki–Miyaura (boron), Negishi (zinc), and Hiyama (silicon) reactions [10]. The selection of ligands has made it possible to utilize a variety of reagents with very simple and inexpensive catalyst precursors. The prominent achievements of nickel catalysis include cyclizations, cycloaddition reactions, and multicomponent couplings.

Based on these observations, our efforts will be directed towards the design of novel reaction methodologies and developing processes for the synthesis of new as well as known bioactive heterocyclic scaffolds using cheaper and cost-effective transition metal catalysts under mild conditions.

8. Study Rationale:

Due to increasingly stringent environmental constraints, there is a great demand by the pharmaceutical and chemical industries to design and development of simple, efficient, and environmentally benign synthetic methods for the construction of bioactive heterocycles. In addition, novel catalytic procedures are necessary to produce the emerging classes of heterocyclic compounds that are becoming the targets of molecular and biomedical research. The proposed topic overcomes most of such drawbacks.

9. Research Methodology:

1. Preparation of transition metal catalysts and optimization of ligands

The preparation of different transition metal catalysts will be achieved by using methods reported in the literature as well as by modifying the literature precedents as per the requirements or nature of the metals and ligands.

2. Synthesis of N,O-containing Heterocycles

Designing the cleaner synthetic routes for different N,O-containing bioactive heterocycles will be carried out by employing one-pot, multicomponent strategies, and mild reaction conditions.

After the selection of target molecules, the synthesis of desired targets will be archived by optimizing reaction conditions, catalysts, ligands, solvents, etc.

Some target molecules are listed below (**Figure 1**):

3. Structural investigations of the synthesized molecules and catalysts

The structures of all the newly synthesized compounds will be confirmed by using different spectroscopic techniques such as UV-Visible, IR, ^{1}H NMR, ^{13}C NMR, 2D NMR X-ray crystallography.

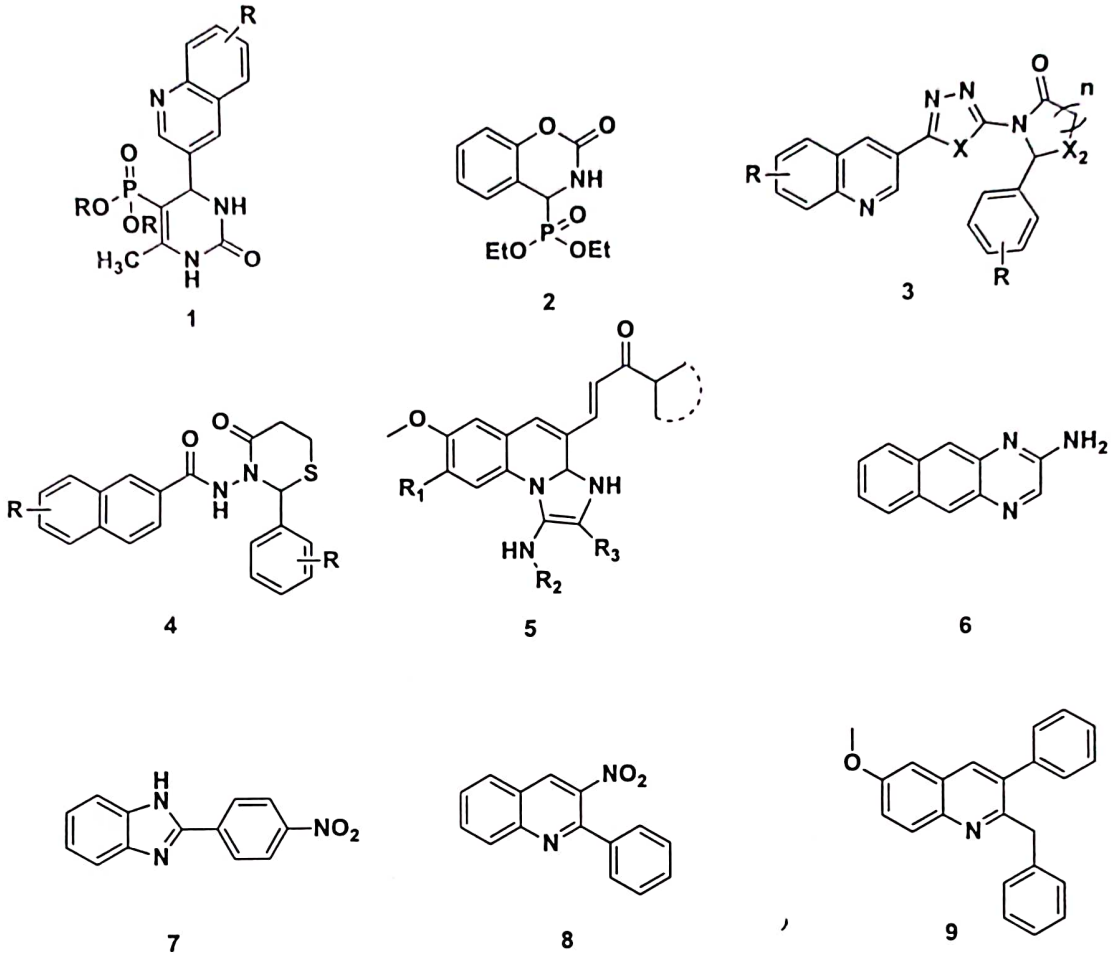

Figure 1: The structures of some proposed heterocycles.

4. Applications

The selected compounds will be screened for their therapeutic potential against various diseases and photophysical properties.

10. Statistical Plan

Months	Plan of Research work
1 to 6	Literature review and Course work
7 to 24	Laboratory work
25 to 30	Result analysis and outcomes
31 to 36	Synopsis and thesis writing

11. Limitations of the Study:

Easy access for the characterization of synthesized compounds.

12. Expected Outcomes of Study

As we will going to develop cleaner, scalable and cost-effective methods for the synthesis of N,O-containing heterocyclic compounds of chemical and pharmaceutical importance using cheap and greener transition metal catalysis.

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